Extended mixed-effect models and growth curves

None of the models finally included random effects after testing them at intercept or/and slope through likelihood ratio test and residual diagnosis (ACF).

Abbreviations:

GA = gestational age in days

I_{18}, I_{21}, and I_{30} = dichotomous variables tagging pregnancies with at least two consecutive ultrasounds performed too short in time (intervals of ≤ 18 days, ≤ 21 days, and ≤ 30 days, respectively).

E [ ] = expected value of each fetal parameter

Femur length (FL)

$$E\,[FL] = [\, -14.674 + 0.208\,GA + 1.210 \cdot 10^{-4}\,GA^2 - 1.204 \cdot 10^{-6}\,GA^3 + 0.018\,\text{maternal age} + 5.793 \cdot 10^{-5}\,GA \cdot \text{maternal height} + 4.139 \cdot 10^{-5}\,GA \cdot \text{paternal height}\,]^{\,1/0.81}$$

The variance function for within-subject errors was modelled as σ^2 multiplied by a power δ of the variance of covariate GA (varPower), allowing for different powers depending on whether the difference in time between two consecutive ultrasounds is ≤ 21 days (I_{21}=1). The estimates obtained for δ were -0.1219 if I_{21}=0 and -0.0368 if I_{21}=1. The exponential correlation structure (*corExp*) was the most adequate within-subject correlation model for FL data.

Supplemental Material, Figure 1. Growth curve of femur length for fetuses from mothers aged 31 years, maternal pre-pregnancy weight = 60 kg, maternal height = 163 cm, paternal height = 175 cm, and time interval between consecutive ultrasounds > 21 days.
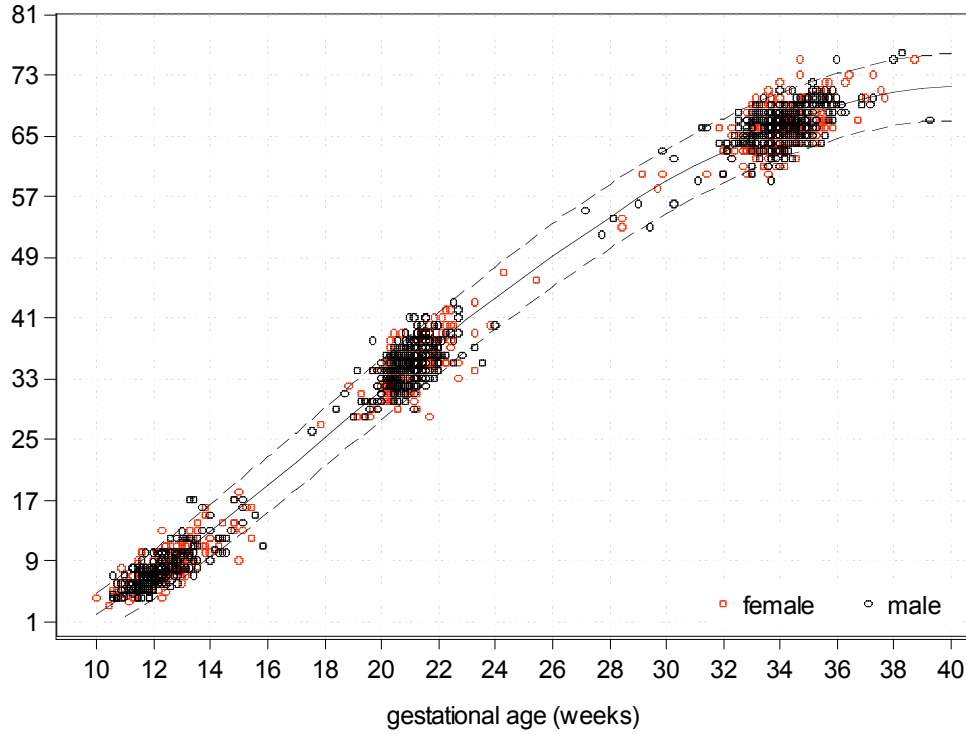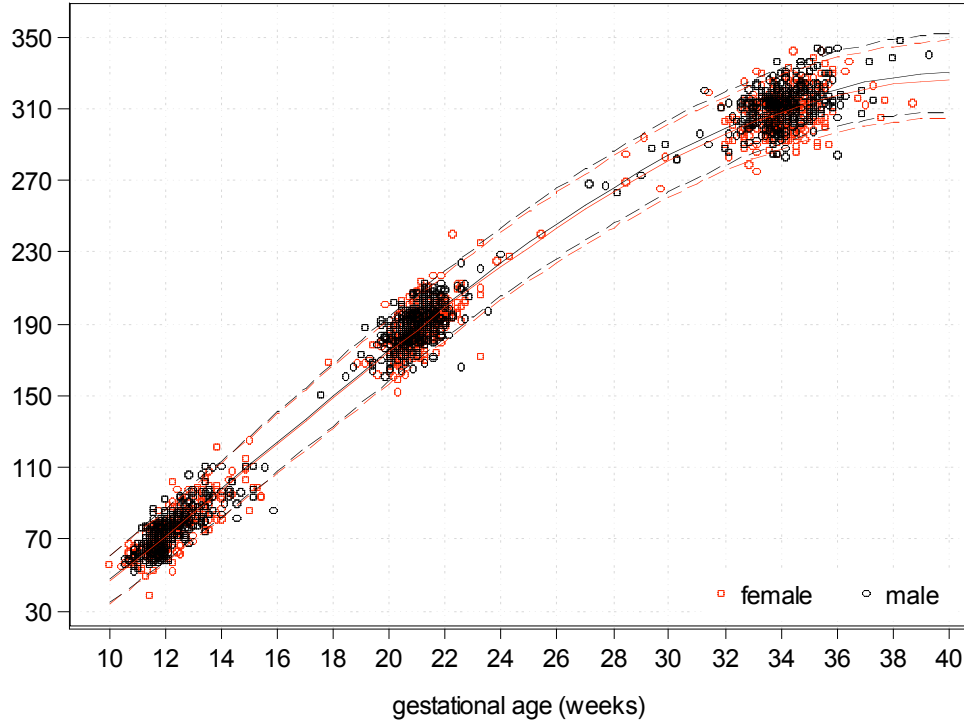

Head circumference (HC)

$$E\,[HC] = [\,-24.847 + 0.555\,\text{GA} -2.877 \cdot 10^{-4}\,\text{GA}^2 -1.701 \cdot 10^{-6}\,\text{GA}^3 + 0.027\,\text{maternal height} +0.027\,\text{maternal age} + 5.895 \cdot 10^{-5}\,\text{GA} \cdot \text{pre-pregnancy weight} + 8.807 \cdot 10^{-5}\,\text{GA} \cdot \text{paternal height} +2.611 \cdot 10^{-3}\,\text{GA} \cdot \text{male}\,]^{\,1/0.76}$$

The variance function for within-subject errors was modelled as σ^2 multiplied by a power δ of the variance of covariate GA, allowing for with different powers depending on whether the difference in time between two consecutive ultrasounds is $\leq$ 30 days (I_{30}=1). The estimates obtained for δ were 1 if I_{30}=0 and 1.3555 if I_{30}=1. The exponential correlation structure (*corExp*) was the most adequate within-subject correlation model for HC data.

Supplemental Material, Figure 2. Growth curve of head circumference for fetuses from women aged 31 years, maternal pre-pregnancy weight = 60 kg, maternal height = 163 cm, paternal height = 175 cm, and time interval between consecutive ultrasounds > 30 days.


Abdominal circumference (AC)

$$E[AC] = [\, -6.274 + 0.213\, GA - 3.075 \cdot 10^{-4}\, GA^2 + 0.157\, male + 0.015\, maternal\ age + 2.558 \cdot 10^{-5} GA \cdot pre\text{-}pregnancy\ weight + 5.366 \cdot 10^{-3}\, GA \cdot paternal\ height\,]^{\,1/0.59}$$

With an exponential correlation structure for within-subjects errors.

Supplemental Material, Figure 3. Growth curve of abdominal circumference for fetuses from women aged 31 years, maternal pre-pregnancy weight = 60 kg, and paternal height = 175 cm.
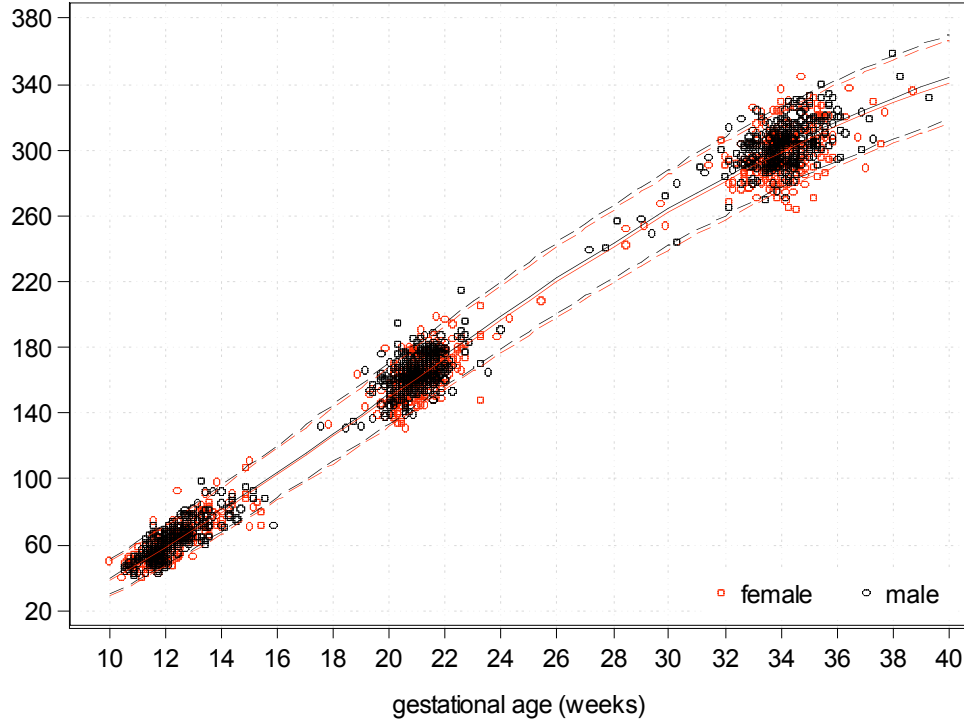
Biparietal diameter (BPD)

$$E[BPD] = [\ -2.061 + 0.096\ GA + 6.170 \cdot 10^{-4}\ GA^2 - 1.909 \cdot 10^{-6}\ GA^3 + 0.071\ 1^{st}\ \text{tertile}$$
of maternal age $+\ 0.156\ 3^{rd}$ tertile of maternal age $+\ 9.180 \cdot 10^{-5}\ GA \cdot$ maternal height
$+1.281 \cdot 10^{-3}\ GA \cdot \text{male}\ ]^{\ 1/0.79}$

Tertiles of maternal age:
1st tertile: 17.28 – 29.08 years
2nd tertile: 29.09 – 32.65 years (reference)
3rd tertile: 32.66 – 42.48 years

The variance function for within-subject errors was modelled as σ^2 multiplied by a power δ of the variance of GA (*varPower*), allowing for different powers depending on gender. The estimates obtained for δ were 1 if male and 1.0661 if female.

Supplemental Material, Figure 4. Growth curve of biparietal diameter for fetuses from women in the 2nd tertile of age and height = 163 cm.
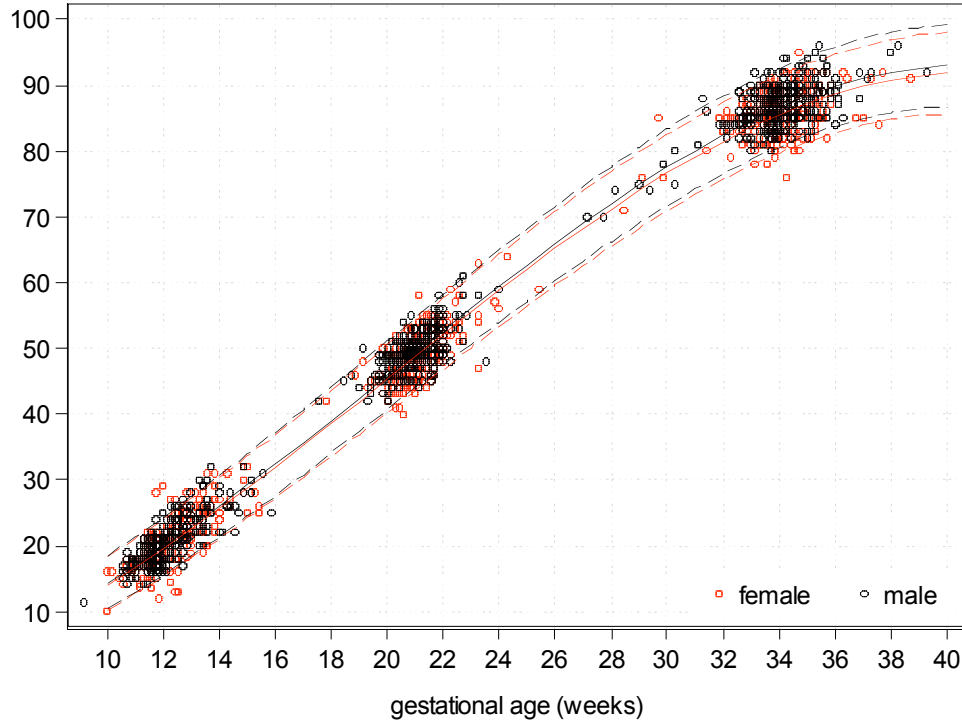

Estimated fetal weight (EFW)

$E\,[EFW] = [1.062 + 1.800 \cdot 10^{-3}\,GA + 6.750 \cdot 10^{-6}\,GA^2 - 0.024 \cdot 10^{-6}\,GA^3 + 2.280 \cdot 10^{-4}$ maternal age $+1.920 \cdot 10^{-3}$ male $+ 0.00008$ maternal age $+0.284 \cdot 10^{-6}\,GA \cdot$ pre-pregnancy weight $+0.499 \cdot 10^{-6}\,GA \cdot$ paternal height] $^{1/0.06}$

The variance function for within-subject errors was modelled as σ^2 multiplied by a power δ of the variance of covariate GA (*varPower*), allowing for different powers depending on whether the difference in time between two consecutive ultrasounds is ≤ 30 days (I_{30}=1). The estimates obtained for δ were 1 if $I_{30} = 0$ and 1.2241 if $I_{30} = 1$. The exponential correlation structure (*corExp*) was the most adequate within-subject correlation model for EFW data.

Supplemental Material, Figure 5. Growth curve of estimated fetal weight for fetuses from women aged 31 years, maternal pre-pregnancy weight = 60 kg, maternal height = 163 cm, paternal height = 175 cm, and time interval between consecutive ultrasounds > 30 days.
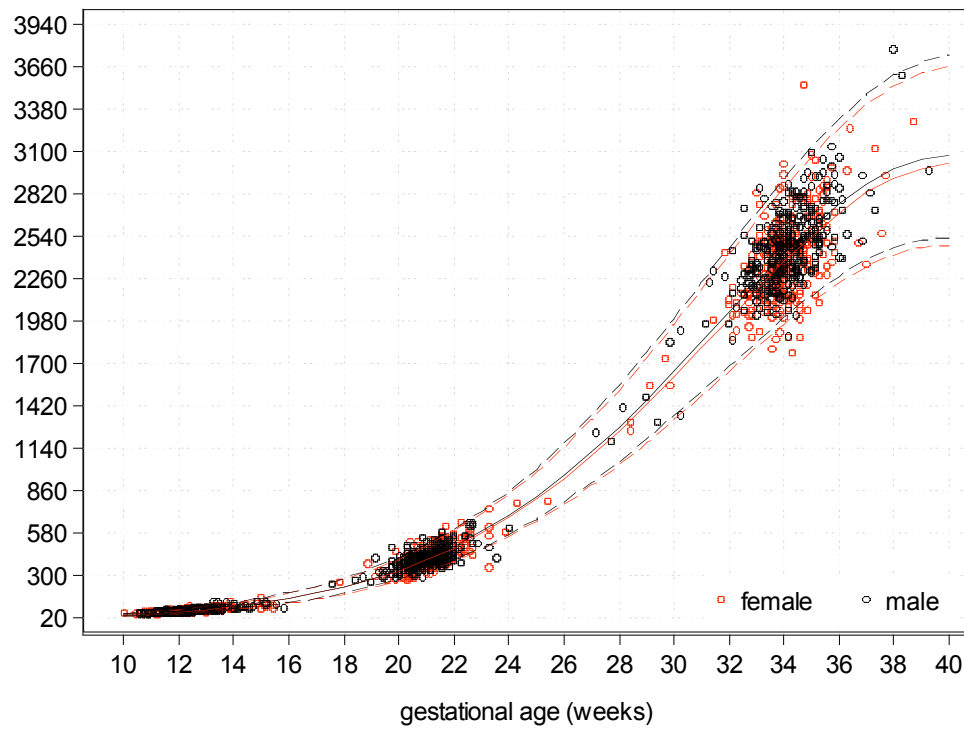
Supplemental Material, Table 1. Adjusted[a] change (coefficient) in fetal parameters for an IQR increase ($\mu g/m^3$) in exposure to NO_2 and BTEX between weeks 1-12 (first trimester), weeks 12-20 (second trimester), and weeks 20-32 (third trimester).

First trimester ultrasound measurements

	No.	NO_2 (weeks 1 – 12)	95% CI	BTEX (weeks 1 – 12)	95% CI
FL (mm)	491	-0.04	-0.20 to 0.12	-0.03	-0.24 to 0.18
HC (mm)	492	0.17	-0.68 to 1.03	0.26	-0.88 to 1.40
AC (mm)	477	-0.19	-0.93 to 0.56	0.01	-0.99 to 1.02
BPD (mm)	531	0.14	-0.09 to 0.38	0.14	-0.18 to 0.46
EFW (g)	474	-0.18	-1.04 to 0.69	0.06	-1.11 to 1.22

Second trimester ultrasound measurements

	No.	NO_2 (weeks 12 – 20)	95% CI	BTEX (weeks 12 – 20)	95% CI
FL (mm)	538	0.04	-0.15 to 0.24	0.03	-0.28 to 0.33
HC (mm)	533	0.64	-0.25 to1.54	1.26	-0.11 to 2.63
AC (mm)	537	0.60	-0.32 to 1.52	0.66	-0.77 to 2.08
BPD (mm)	538	0.33	0.00 to 0.66	0.35	-0.01 to 0.71
EFW (g)	535	3.16	-1.97 to 8.28	1.57	-6.38 to 9.51

Third trimester ultrasound measurements

	No.	NO_2 (weeks 20 – 32)	95% CI	BTEX (weeks 20 – 32)	95% CI
FL (mm)	537	0.02	-0.21 to 0.24	0.02	-0.28 to 0.32
HC (mm)	536	0.17	-0.93 to 1.27	0.81	-0.66 to 2.27
AC (mm)	536	0.18	-1.11 to 1.47	0.29	-1.44 to 2.02
BPD (mm)	535	0.11	-0.20 to 0.41	0.04	-0.38 to 0.45
EFW (g)	532	3.36	-19.74 to 26.46	3.07	-27.84 to 33.97

IQR, interquartile range

[a] Adjusted for gestational age (allowing for polynomial terms), sex, season of conception, parity, maternal education, tobacco smoking, and maternal and paternal weight and height.